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Post-Inflammatory Nephropathy

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1. Introduction

Post-inflammatory nephropathy is a progressive renal scarring which may be a consequence of one or more episodes of acute pyelonephritis.

Macroscopically, post-inflammatory nephropathy leads to gradual decrease in kidney size and deformity and dilation of pelvicalyceal system. These alternations are due to tubulointerstitial fibrosis and glomerular sclerosis followed by renal parenchymal atrophy and kidney cirrhosis development (Bernstein, 1994). It was demonstrated that there was positive correlation between severity of renal scarring and loss of renal function (Eddy et al., 2000; Eddy, 2000).

Post-inflammatory nephropathy is the leading cause of end-stage renal failure. In Europe, children with end-stage renal failure due to post-inflammatory nephropathy constitutes 10-24% of those on renal replacement therapy (Broyer et al., 1993).

The development of post-inflammatory nephropathy is influenced by age and gender of patient, the number of acute pyelonephritis episodes, the presence of anatomical and/or functional urinary system abnormalities, the virulence of invading pathogen, the time of appropriate treatment initiation and genetic predisposition.

The majority of studies demonstrated that the risk of renal scarring decreases with age and is highest in children in the first year of life (Hansson et al., 1999; Vernon et al., 1997; Arant, 1991; Benador et al., 1997; Smellie et al.,1998; Sheu et al., 2009). This may be related to the correction of anatomical and/or functional urinary system abnormalities and the decrease in susceptibility of renal parenchyma to infection due to defense mechanisms maturation (Benador et al., 1997; Rushton et al.,1992). Dissimilar results were obtained by Pecile et al. (2009). The authors showed that the lowest risk of renal scarring after first episode of febrile urinary tract infection was in children in the first year of life and the highest one - in children aged 5 -14 years.

It was also demonstrated that the male gender is an independent risk factor for renal scarring (Silva et al., 2009; Mohanan et al., 2008).

The risk of post-inflammatory nephropathy development increases with the number of acute pyelonephritis episodes. Renal scarring develops in 15% of children after the first episode of acute pyelonephritis. After two episodes of acute pyelonephritis renal scarring occurs in 35% of children and after three or more episodes – in 60% of children. The study by Orellana et al. (2004) showed that one episode of pyelonephritis caused permanent renal parenchymal injury in 55.9% of children whereas recurrent urinary tract infection – in 72.6% of children.

Anatomical and functional abnormalities of urinary system particularly predispose to post-inflammatory nephropathy development, although renal scarring may occur after acute pyelonephritis in children without these abnormalities (Gordon et al., 1987; Vanderfaeillie et al., 1998).

Numerous studies emphasized the significance of invading pathogen virulence for post-inflammatory nephropathy development. P, I and F1C fimbriae of *Escherichia coli* give rise to secretion of interleukins 6 and 8 by uroepithelial cells (Backhed et al., 2001; Hedlund et al., 1996, 2001). In addition, lipopolysaccharides of Gram-negative bacteria stimulate the release of cytotoxic nitric oxide and proinflammatory cytokines (Backhed et al., 2001; De Man et al., 1989; Traylor & Mayeux, 1997) whereas lipid A stimulates synthesis of nitric oxide (Traylor & Mayeux, 1997). Alfa-hemolysins of *Escherichia coli* give rise to cytolysis (Uhlen et al., 2000) and induce apoptosis of tubular cells (Chen et al., 2003, 2004].

Immediate initiation of appropriate therapy is of utmost importance in prevention of renal scarring development. Antibacterial treatment initiated within 24 hours prevents migration of neutrophils to inflammatory foci (Ransley & Risdon, 1981). A delay in initiation of therapy increases the risk of renal scarring from 5% to over 15%.

In numerous studies, the importance of genetic predisposition to renal scarring was emphasized. An association between polymorphism of angiotensin-converting enzyme gene and renal scarring was demonstrated (Haszon et al., 2002; Hohenfellner et al., 1999; Ohtomo et al., 2001; Ozen et al., 1999; Pardo et al., 2003). Similarly, polymorphism of transforming growth factor β gene (Kowalewska-Pietrzak et al., 2008; Hussein et al., 2010) and polymorphism of vascular endothelium growth factor gene (Hussein et al., 2010) had impact on severity of renal scarring.

Post-inflammatory nephropathy may be classified into reflux nephropathy due to vesico-ureteral reflux and obstructive nephropathy due to urinary tract obstruction (Marra et al., 2004; Orikasa et al., 1995; Smellie et al., 1981).

2. Pathogenesis of post-inflammatory nephropathy

Pathogenesis of post-inflammatory nephropathy is complex and not fully understood (Fig.1). In the last years, the investigators paid particular attention to the role of molecular factors in initiation and progression of post-inflammatory nephropathy. Numerous studies concerning molecular mechanisms leading to renal scarring were published (Eddy, 2000; Eddy et al., 2000; Guroze et al., 2005; Jahnukainen et al., 2005; Lane et al., 2002, Nath, 1998; Solari et al., 2004; Strutz et al., 1995,1996,1999, 2003; Weiss et al., 1994). The process of renal scarring may be divided into four phases: induction, fibrogenic signaling, fibrogenic, and destructive phases (Eddy, 2000). Induction phase is also known as cellular activation and injury phase. The interstitial space is infiltrated by both neutrophils and monocytes. In acute inflammation, the migration of neutrophils is primarily observed whereas in chronic inflammation monocytes predominate.

Neutrophils release numerous cytokines, lysosomal enzymes and free oxygen radicals. In addition, neutrophils may activate fibroblasts directly or indirectly via release of elastase and thus they participate in fibrogenic process (Bailey, 1973; Kishimoto & Harano, 1988).

Monocytes transform into macrophages which also participate in fibrogenic process (Lane et al., 2002; Nath, 1998). Solari et al. (2004) demonstrated that in reflux nephropathy, an increase in number of mastocytes was observed. Mastocytes produce numerous cytokines among others profibrogenic transforming growth factor β (TGF-β) and basic fibroblast

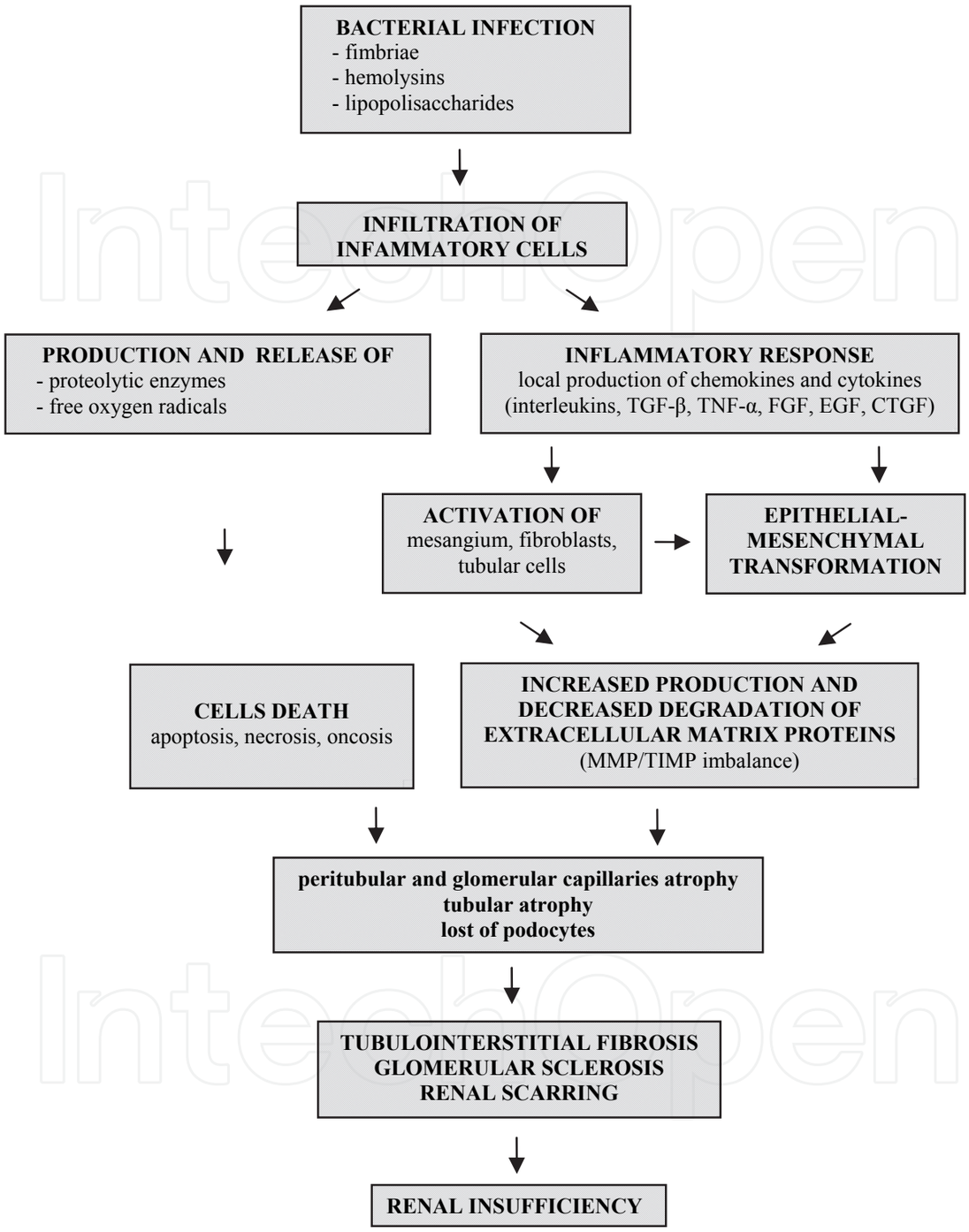

Fig. 1. Pathogenesis of post-inflammatory nephropathy.

growth factor (bFGF). In addition, mastocytes produce enzymes – tryptase and chymase. Tryptase stimulates type I collagen production by fibroblasts whereas chymase releases TGF-β from inactive complexes and converts angiotensin I to angiotensin II. This suggests participation of mastocytes in fibrogenic process.

Inflammatory infiltration cells produce other cytokines such as interleukins 1, 6, 8 (IL-1, IL-6, IL-8) and tumor necrosis factor α (TNF-α).
The study by Wolfs et al. (2002) demonstrated that Toll-like receptors-2,-4 (TLR-2, TLR-4) were responsible for defense response during acute pyelonephritis. Activated by endogenous danger signals TLR-2 expression is also of significance in induction of inflammation during progressive renal injury (Leemans et al., 2009).
During acute interstitial inflammation activated tubular cells directly participate in activation of myofibroblasts and fibroblasts (Abbate et al., 2002; Alpers et al., 1994; Roberts et al., 1997) and produce monocyte chemoattractant protein-1 (MCP-1) (Okada et al., 2000), endothelin-1 (ET-1) (Bruzzi et al., 1997), angiotensin II causing vasoconstriction, and transferrin (Chen et al., 1998) activating free oxygen radicals (Chertin et al., 2002).
As a result of acute interstitial inflammation expression of novel antigens on tubular cells occurs and these new antigens stimulate an immune response of lymphocyte T which enhances inflammation and progression of nephropathy (Szeto et al., 2005).
In addition, tubular cells and fibroblasts transform into myofibroblasts. This process is called epithelial-mesenchymal transformation or transition (EMT). Numerous authors confirmed the possibility of EMT (Oldfield et al., 2001; Rastaldi et al., 2002; Strutz et al., 1995; Zeisberg et al., 2001). Myofibroblast, unlike typical interstitial fibroblasts, are characterized by their expression of the myocyte protein α-smooth muscle actin. These cells are considerably more profibrotic than interstitial fibroblasts.
During acute interstitial inflammation activation of complement system via classic and alternative pathway is also observed. C3a and C5a component are known to be chemotactic for monocytes. There is evidence for participation of complement system in inflammatory infiltration formation, tubular atrophy and tubulointerstitial fibrosis (Nangaku et al., 1999).
In pathogenesis of chronic interstitial inflammation leukocyte adhesion molecules such as integrins, selectins and members of the immunoglobulin superfamily (intercellular adhesion molecules – ICAMs and vascular cell adhesion molecules – VCAMs) seem to play a crucial role but details remain unclear. ICAMs, VCAMs and osteopontin are chemoattractant for monocytes (Okada et al., 2000; Ricardo et al., 1996).
An early phase of acute interstitial inflammation is reversible provided that nociceptive factor is eliminated (Eddy, 2000; Eddy et al., 2000).
In fibrogenic signaling phase, numerous fibrogenic factors are released, including TGF-β1, tissue growth factor (TGF), angiotensin II, ET-1, platelet growth factor (PDGF-BB), bFGF, TNF-α, and IL-1. Fibrogenic factors activate their cognate receptors expressed by tubulointerstitial cells and subsequent extracellular matrix accumulation along tubular basement membranes and within the interstitial space occurs.
In fibrogenic phase, fibrogenic factors activate a new group of genes that lead to excessive accumulation of extracellular matrix proteins and polysaccharides within the interstitial space (Beck-Schimmer et al., 1998; Pichler et al., 1996). In this phase, disequilibrium between extracellular matrix production and its degradation is observed.
A main cause of impairment of extracellular matrix remodeling and degradation is a decrease in activity of metalloproteinases (MMP) due to induction of tissue inhibitors of metalloproteinases (TIMP). Four major TIMP have been identified (TIMP-1, TIMP-2, TIMP-3, and TIMP-4). In the majority of progressive renal diseases, marked induction of TIMP-1 is observed (Chromek et al., 2003,2004; Eddy et al., 2000; Kim et al., 2001). Within kidney, TIMP-1 is produced by tubular cells, fibroblasts and macrophages. Production of TIMP-1 is stimulated by growth factors (TGF-β1, TGF-α, epithelial growth factor (EGF), PDGF, TNF-

α), interleukins (IL-1, IL-6, IL-10), oncostatin M, endotoxin and thrombin. Recently, the induction of plasminogen activator inhibitor-1 (PAI-1) in progressive renal diseases was documented. This may suggest its participation in tubulointerstitial fibrosis. PAI-1 is produced by tubular cells, fibroblasts and myofibroblasts. Its expression is induced by TGF-β, EGF, PDGF, TNF-α and bFGF (as cited in Eddy, 2000).

In destructive phase, a gradual loss of functioning nephrons occurs as a result of excessive accumulation of extracellular matrix. Glomerular sclerosis, peritubular capillaries and tubular atrophy lead to progressive renal failure (Orphanides et al., 1997; Seron et al., 1990). TGF-β, TNF-α, IL-1β, IL-6 and IL-8 seem to play a major role in renal scarring.

Transforming growth factor β (TGF-β)

TGF-β is released primarily by macrophages, neutrophils, lymphocytes and platelets. TGF-β is produced as an inactive complex with LAP (*latent associated protein*) and LTBP (*latent TGF-β binding protein*) which are components of extracellular matrix. These proteins have potential to store and release of TGF-β. Five isoforms of TGF-β (TGF-β 1-5) have been identified. In mammalians, only TGF-β 1-3 are found. Active TGF-β is a homodimeric 25kD protein. Within kidneys numerous factors increase TGF-β expression, including angiotensin II, endothelin I, interleukin 1β, platelet activating factor (PAF), thromboxane, thrombospondin, glucose, insulin, atrial natriuretic peptide (ANP), secreted protein acidic and rich in cysteine (SPARC), and hypoxia (Pichler et al., 1996). Increased TGF-β expression in kidneys is also caused by TNF-α and connective tissue growth factor (CTGF) (Zhang et.al., 2004). In addition, proteoglycans accumulated within the interstitial space may be a reservoir of TGF-β.

TGF-β stimulates production of proinflammatory cytokines (IL-1, IL-6, IL-8 and TNF-α). It is known to be chemotactic for monocytes, neutrophils, and fibroblasts. TGF-β stimulates production of extracellular matrix proteins such as fibronectin, collagen and proteoglycans. In addition, it increases expression of TIMPs. This contributes to depressed activity of MMP and stabilization of extracellular matrix (Boettinger & Bitzer, 2002; Boettinger et al., 1997; Broder et al., 1994; Cotton et al., 2002; Deng et al., 2006; Fan et al., 1999; Goumneos et al., 2002; Guo et al., 1997; Jahnukainen et al., 2005; Korzon et al., 2004; Lane et al., 2002; Liapis, 2003). Poncelet & Schnaper (1998) documented that TGF-β stimulates production of collagen I, III and IV by mesangial cells. Experimental studies on transgenic mice showed that overexpression of TGF-β resulted in glomerular and interstitial fibrosis (Kelly et al., 1999). In experimental model of ureteral obstruction (Shinozaki et al., 1998) and in proteinuric state (Jernigan et al., 1996), overexpression of the type II receptor for TGF-β gave rise to increased accumulation of collagen within the interstitial space.

TGF-β induces EMT (Fan et al., 1999; Ng et al., 1998) and inhibits apoptosis of myofibroblasts (Zhang & Phan,1999; Fan et al., 1999; Frazier et al., 2000). In addition, TGF-β induces apoptosis of endothelial cells. This results in peritubular and glomerular capillaries atrophy followed by fibrosis (Choi & Ballermann, 1995; Kang et al., 2002; Ohashi et al., 2000). TGF-β is also known to induce apoptosis of tubular cells leading to tubular atrophy with subsequent fibrosis (Dai et al.,2003; Gobe & Axelsen,1987; Kopp et al., 1996; Lane et al., 2002; Ortiz et al., 1997; Sanderson et al., 1995).

Experimental studies demonstrated increased TGF-β mRNA expression during infection with *Escherichia coli* (Khalil et al., 2000). Increased urinary TGF-β excretion was showed in children with urinary tract infection (Farmaki et al., 2005).

An association between TGF-β gene polymorphism and susceptibility to renal scarring was observed. Solari et al. (2005) documented that the risk of reflux nephropathy was higher in

patients with -509CT and Leu10Pro genotypes. Khalil et al. (2005) showed that homozygosity for -509T and Arg25 resulted in more rapid progression of renal failure whereas patients with -800GA genotype were less susceptible to renal scarring (Cotton et al., 2002).

Numerous studies confirmed a significant participation of TGF-β in pathogenesis of obstructive nephropathy (Blom et al., 2001; Chevalier, 2004; Duncan et al., 1999; Kaneto et al., 1999; Klahr & Morrissey, 1998, 2002, 2003; Sato et al., 2003; Schnaper et al., 2003). In this type of nephropathy, increased angiotensin II production is observed and angiotensin II enhances TGF-β expression. Thus angiotensin II plays a key role in initiating of tubulointerstitial fibrosis in obstructive nephropathy. Recently, in patients with ureteropelvic junction obstruction, increased urinary TGF-β excretion was observed (Almodhen et al., 2009, Sager et al., 2009).

Tumor necrosis factor α (TNF-α)

TNF-α also known as cachectin is produced by several cells within kidneys, including proximal tubular cells, mesangial cells, interstitial fibroblasts and macrophages. The most potent stimulus for TNF-α production is lipopolysaccharides of Gram-negative bacteria. TNF-α stimulates production of proinflammatory cytokines (IL-1 and Il-6) by macrophages and increases macrophages cytotoxicity. In addition, it is known to be chemotactic for fibroblasts and stimulates their proliferation. TNF-α has also antifibrotic effects because it enhances collagenase activity and inhibits collagen gene expression. In addition, TNF-α diminishes activity of TIMP and increases production of latent MMP-9 (Nee et al., 2004).

Profibrogenic effects of TNF-α was confirmed in study by Guo et al. (1999). The authors demonstrated less severe renal scarring in mice genetically deficient of receptors specific for TNF-α. In addition, TNF-α contributes to renal scarring by releasing IL-1β and TGF-β from inflammatory infiltration cells (Jahnukainen et al., 2005). Recently, experimental study demonstrated less severe renal scarring in rats with nephritis when monoclonal antibodies against TNF-α were administered (Khan et al., 2005). Wolfs et al. (2002) showed that TNF-α induced overexpression of TLR-2 and -4. TNF-α contributes to the development of obstructive nephropathy. Overexpression of TNF-α is due to increased angiotensin II secretion observed in upper urinary tract obstruction.

Interleukin 1 (IL-1)

IL-1 is one of the major regulator inflammatory and immune reactions. It may be produced by several cells within the kidney, including macrophages, mesangial cells, endothelial cells and macrophages. It is also known to be chemotactic for neutrophils and monocytes. Other activities of IL-1 include: - stimulation of production of IL-1, IL-6, IL-8 and TNF-α by macrophages, - stimulation of production of IL-6 and collagenase by fibroblasts, - stimulation of fibroblast proliferation and possibly of extracellular matrix production, - activation of endothelial cells, - induction of smooth muscle cells lysis. Fibrosis-promoting effects of IL-1 were also demonstrated (Ichino et al., 2008, Mittal et al., 2009). It also inhibits MMP-9 activity which degrades type IV collagen of extracellular matrix and diminishes activity of IL-1 receptor antagonist (IL-1Ra).

Vesey et al. (2002, 2002) demonstrated that IL-1β stimulated proliferation of interstital fibroblast and enhanced production of type I collagen, fibronectin, TGF-β and nitric oxide.

Study by Zang et al. (2005) showed that IL-1β induced transformation of tubular cells into myofibroblasts. In addition, IL-1β stimulates production of IL-6 and IL-8. This intensifies inflammation and promotes interstitial fibrosis (Lonnemann et al., 1995).

Kassem et al. (2005) demonstrated increased urinary IL-1β excretion in children with acute pyelonephritis. The authors also revealed positive correlation between urinary IL-1β and IL-8 excretion. The survey by Wetmore et al. (2005) showed an association between IL-1 gene polymorphism and occurrence of chronic renal diseases which resulted in impairment of renal function. Elevated urinary IL-1β excretion was demonstrated in patients with chronic renal failure. The highest urinary IL-1β excretion was observed in pre-dialysis patients. In those patients, considerably higher plasma IL-1Ra level as compared to controls was disclosed (Pereira et al., 1994).

Interleukin 6 (IL-6)

IL-6 is produced by several cells within kidney, including macrophages, interstitial fibroblasts and endothelial cells. The study by Patel et al. (2005) demonstrated that IL-6 intensified inflammation and impaired renal function. Increased urinary IL-6 excretion in children with urinary tract infection and positive correlation between urinary IL-6 excretion and severity of proteinuria, hematuria and pyuria were also observed (Benson et al., 1996; Gendrel et al., 1998; Jantausch et al., 2000; Nicolle et al, 1993; Otto et al., 1999; Mizuano et al., 2001). Experimental studies revealed increased expression of renal IL-6 in mice with acute pyelonephritis due to ureteral obstruction (Kabore et al., 1999; Rugo et al., 1992) and increased serum IL-6 level in the majority of mice with acute pyelonephritis (Rugo et al., 1992). Khalil et al. (2000) demonstrated increased mortality in mice with acute pyelonephritis and IL-6 deficiency. The authors also disclosed more severe histopathological changes in kidneys of IL-6 deficient mice. Numerous studies demonstrated that urinary IL-6 excretion was higher in patients with acute pyelonephritis than in those with asymptomatic bacteriuria (Benson et al., 1994; Hedges et al., 1992; Kassem et al., 2005; Ko et al., 1993; Ohta et al., 1992; Otto et al., 1999; Roilides et al., 1999). Positive correlation between urinary IL-6 excretion and the risk of renal scarring was also disclosed (Benson et al., 1996; Jacobson et al., 1998; ; Roilides et al., 1999; Tullus et al., 1994). Wang et al. (2001) observed significant correlation between urinary IL-6 excretion and renal scars diagnosed by static renoscintigraphy in children with vesicoureteral reflux. In those children, there were positive correlations between urinary IL-6 excretion and serum α1- microglobulin, β2-microglobulin, creatinine levels and urinary albumin excretion. These authors (Wang et al., 2001) also performed immunohistochemical evaluation of specimens obtained from removed scarred kidneys. Overexpression of IL-6 in renal tubules and scars was observed. Data on serum IL-6 level in patients with urinary tract infection and post-inflammatory nephropathy are scarce and conflicting. Smółko et al. (2004) revealed higher serum IL-6 level in children with vesicoureteral reflux of high grade as compared to controls. The study by Gokce et al. (2010) showed the similar results. Increased serum IL-6 level was observed primarily in patients with febrile urinary tract infection (Benson et al., 1994; Hedges et al., 1991,1992; Jacobson et al., 1994, 1998).

IL-6 gene polymorphism influenced susceptibility to urinary tract infections but had no effect on renal parenchymal scarring (Cotton et al., 2000).

Interleukin 8 (IL-8)

Within kidney IL-8 is produced primarily by macrophages, interstitial fibroblasts, tubular and endothelial cells. It has bactericidal and pro-inflammatory activity because it causes chemotaxis and degranulation of neutrophils. In patients with acute urinary tract infection and post-inflammatory nephropathy, increased serum IL-8 level and increased urinary IL-8

excretion were observed (Kassem et al., 2005; Tikhonov et al., 1997; Haraoka et al., 1996). Increased urinary IL-8 excretion is thought to be a marker of vesicoureteral reflux and post-inflammatory nephropathy (Galanakis et al., 2006; Gokce et al., 2010; Haraoka et al., 1996; Smółko et al., 2004). Taha et al. (2003) demonstrated increased urinary IL-8 excretion in patients with acute and chronic urinary tract infections. The authors also disclosed higher urinary IL-8 excretion in females as compared to males and positive correlation between urinary IL-8 excretion and markers of inflammation, including leukocytosis and serum C-reactive protein level.

In patients with urinary tract infection, increased urinary IL-8 excretion was observed in numerous studies (Jacobson et al., 1994; Kassem et al., 2005; Nicolle et al., 1993; Olszyna et al., 2000; Otto et al., 1999; Rao et al., 2001; Sheu et al., 2009; Tullus et al., 1994). Roilides et al. (1999) and Ko et al. (1993) revealed increased urinary IL-8 excretion in newborns with abnormal static renoscintigraphy result. Increased urinary IL-8 excretion was also revealed in patients with chronic pyelonephritis (Rebenok et al., 1999; Tikhonov et al., 1997). Experimental studies in mice and rabbits with urinary tract infection and without or mutated IL-8 receptor disclosed more severe course of infection, massive renal scarring and considerable impairment of renal function (Frendeus et al., 2001; Hang et al., 2000). The authors suggested that overproduction of IL-8 promoted clearance of bacteria from kidneys and thus diminished the risk of renal scarring. There is an opinion that overproduction of IL-8 in response to urinary tract infection results in univocal and distinct symptoms leading to prompt diagnosis and early initiation of appropriate treatment and thus diminishes the risk of renal scarring (Jahnukainen et al., 2005).

2.1 Reflux nephropathy

Reflux nephropathy (RN) refers to renal scarring due to vesicoureteral reflux. Chronic renal failure as a result of RN is observed in 5%-40% of children aged below 16 years and in 5%-20% of adults (Kenda et al., 1997; Noe, 1992; Wan &Greenfield, 1996). RN is also a frequent cause of end-stage renal failure.

Vesicoureteral reflux is a back-flow of urine from the bladder into the ureter and pelvicalyceal system. The back-flow of urine from pelvicalyceal system into collecting ducts is called intrarenal reflux. When urine is infected, intrarenal reflux results in renal infection. The prevalence of intrarenal reflux is particularly high in children aged below 5 years. In 1960, Hodson and Edwards (as cited in Sieniawska & Wyszyńska, 2003) first demonstrated that there was association between vesicoureteral reflux and chronic pyelonephritis. Antenatal renal damage due to vesicoureteral reflux may also develop (Arant, 1991; Bailey, 1973; Lerner, 1994; Smellie, 1975; Peters & Rushton, 2010).

Classification of grades of vesicoureteral reflux according to International Reflux study Committee, (1981) is showed on Fig. 2.

Vesicoureteral reflux may be primary or secondary. Primary vesicoureteral reflux is due to congenital abnormal lateralization of ureteral orifice. Secondary vesicoureteral reflux is a result of anatomical and/or functional abnormalities of lower urinary tract.

Primary vesicoureteral reflux is the most common congenital abnormality of urinary system and is diagnosed in 20% - 60% of children with urinary tract infection (Ataei et al., 2004; Zajaczkowska et al., 2001; Alvarez et al., 2009). In the noninfected general population, the prevalence of vesicoureteral reflux is 1% -2% and in siblings of children with vesicoureteral reflux and urinary tract infection – 5% -50% (Noe, 1992).

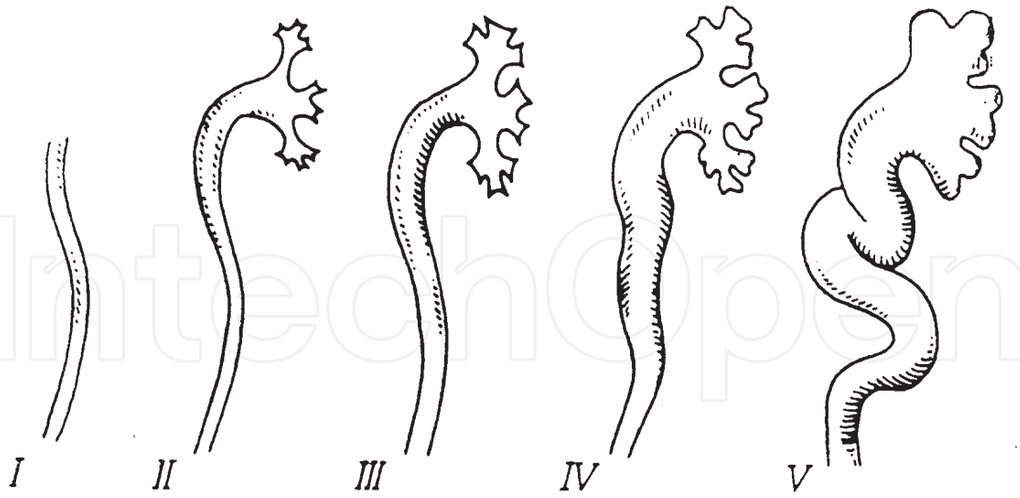

Fig. 2. The International Reflux Study classifies reflux grades as follows: I) reflux into ureter only; II) reflux into ureter, pelvis, and calyces, no dilation, normal calyceal fornices; III) mild or moderate dilation and/or tortuosity of the ureter and mild or moderate dilation of renal pelvis but no or little blunting of the fornices; IV) moderate dilation and/or tortuosity of the ureter and moderate dilation of the renal pelvis and calyces V) gross dilation and tortuosity of the ureter and gross dilation of the renal pelvis and calyces. Papillary impressions are no longer visible in the majority of calyces. There is complete obliteration of the sharp angle of the fornices, but maintenance of papillary impressions in major calyces.

Relation between urinary tract infection, vesicoureteral reflux and renal scarring has been known since a long time (Bailey, 1973; ; Kincaid-Smith,1975; Smellie et al., 1975; Van den Abbeele et al., 1987). In the early 1970s, Bailey (1973) coined the term "reflux nephropathy" to describe renal scarring in patients with vesicoureteral reflux. The study by Sheikh et al. (2010) confirmed higher risk of renal scarring in patients with vesicoureteral reflux. Orellana et al. (2004) demonstrated that prevalence of renal scarring is higher in children with vesicoureteral reflux than in those without that anomaly (72% versus 52%). In addition, it was revealed significant association between vesicoureteral reflux diagnosed after first episode of urinary tract infection and chronic renal failure (Marra et al., 2004).
Previously, vesicoureteral reflux was thought to be an independent risk factor for renal scarring. Nowadays, this hypothesis is questioned. However, an association between urinary tract infection in children with vesicoureteral reflux and renal scarring remains unquestionable (Faust et al., 2009; Jahnukainen et al., 2005; Muinuddin et al., 2008). This was confirmed by recent studies that demonstrated an increase in the risk of renal scarring after acute pyelonephritis in patients with vesicoureteral reflux (Kanellopoulos et al., 2006; Lee et al., 2006; Polito et al., 2006; Oh et al., 2008). Studies by Svensson et al. (2005) and Mohanan et al. (2008) disclosed that renal scarring was detected less frequently in infants with vesicoureteral reflux and without urinary tract infection than in those with vesicoureteral reflux and urinary tract infection. In study by Ylinen et al. (2003) renal scarring was found more frequently in infants in whom vesicoureteral reflux was diagnosed after the first episode of urinary tract infection than in those in whom vesicoureteral reflux was detected antenatally. The risk of acute pyelonephritis and thus renal scarring increases along with grade of vesicoureteral reflux (Arant, 1991; Oh et al., 2008, Shaikh et al., 2010, Silva et al.,

2010) because vesicoureteral reflux of high grade occurs throughout micturition in contrast to vesicoureteral reflux of low grade which occurs only at the peak of micturition (Jacobsson et al., 1992).

In the last years, an association between ACE gene polymorphism and development/ progression of RN was demonstrated. The D allele of ACE gene polymorphism was associated with higher converting enzyme activity and thus higher concentration of angiotensin II in plasma and tissues. This resulted in more rapid development and progression of RN (Haszon et al., 2002; Hohenfellner et al., 1999; Ohtomo et al., 2001; Ozen et al., 1999). Some studies questioned the significance of ACE gene polymorphism as an independent risk factor for the development and progression of RN (Dudley et al., 2002; Pardo et al., 2003). An association between TGF-β1 gene polymorphism and the risk of renal scarring in patients with vesicoureteral reflux was also disclosed Kowalewska-Pietrzak et al. (2008), whereas Hussein et al. (2010) demonstrated an association between vascular endothelium growth factor (VEGF) gene polymorphism and the risk of the development of RN.

2.2 Obstructive nephropathy

Obstructive nephropathy (ON) refers to renal scarring due to mechanical obstruction to urine flow (Liapis, 2002).

Obstruction to urine flow may be congenital or acquired. It can occur at any level of urinary tract, including renal tubules, renal pelvis, ureters, bladder and urethra. Obstruction to urine flow most commonly occurs at ureteropelvic junction (Koff, 1990; Norbeck et al., 1993). The severity of obstructive nephropathy depends on severity of obstruction, its location and duration, age of occurrence and concomitant infection.

Complete or severe obstruction to urine flow leads to obstructive nephropathy more rapidly than incomplete one. In addition, the higher the obstruction is located the more severe obstructive nephropathy develops. Age of patient is of great significance. Fetal and neonatal kidneys are at greatest risk for damage. Antenatal urinary tract obstruction disturbs kidney development and results in polycystic dysplasia or hypodysplasia (Chevalier, 2004).

Re-expression of Pax-2 (Li et al., 2010) gene and decreased expression of Bcl-1 gene (Zhang et al. 2001) enhance susceptibility to the development of obstructive nephropathy.

In the development and progression of obstructive nephropathy, primarily cytokines and vasoactive substances are implicated (Chevalier, 2004; Chevalier et al., 2009; Chiou et al., 2004; Grande et al.,2010; Klahr, 2001; Klahr & Marrissey, 1998, 2002, 2003; Rice et al., 2004). Nowadays, TGF-β1 and TNF-α are thought to play a crucial role in renal damage. Obstruction to urine flow and alternations in intra- renal hemodynamics result in increased secretion of angiotensin II which in turn enhances TGF-β1 and TNF-α expression (Grande et al., 2010; Leonova et al., 2007; Manucha, 2007; Padillo et al., 2007; Pimentel et al., 1995; Sager et al., 2009; Wang et al.,2010). Due to urine stasis urinary tract infection may develop. Infection is an additional factor which causes renal damage.

Bilateral complete or severe urinary tract obstruction are the most dangerous anomalies. In this clinical settings, even early surgery does not always protect kidneys from permanent damage leading to end stage renal failure during childhood (Chevalier et al., 2000). Patients after surgical correction of urinary tract obstructions requires careful monitoring in order to early detect of obstructive nephropathy symptoms and initiation of nephroprotective therapy.

3. History and clinical manifestations of post-inflammatory nephropathy

The clinician needs to obtain a detailed history about the type and duration of symptoms. Most often there is a history of recurrent urinary tract infections which cease or occur less frequently after surgical correction of anatomical anomaly, appropriate therapy of functional disturbances of lower urinary tract and/or antibacterial prophylaxis. Severe and developed early in life post-inflammatory nephropathy leads to dwarfism and body weight deficit (Polito et al., 1999; Seidel et al., 1993). The patient may complain of loin or abdominal pain which may be a result of urinary tract infection, dilation of urinary tract due to obstruction or urolithiasis secondary to urine stasis. The patient should be asked questions about difficulty initiating urination, decreases in the force of urine stream, posturination dribbling, and incomplete emptying. In addition, the patient should be questioned about nocturia as chronic renal failure is characterized by the lack of ability to concentrate urine during the night. Post-inflammatory nephropathy may also be asymptomatic.

20% of children with post-inflammatory nephropathy develop end-stage renal failure before 18th year of age and approximately 50% of them - in the fourth decade of life .

Post-inflammatory nephropathy may lead to arterial hypertension due to ischemia of renal scars and resultant increase in renin production (Wyszynska & Litwin, 2000). Arterial hypertension develops most commonly in patients with diffuse bilateral renal scarring (Hamed et al., 1992; Kohler et al., 1997, 2003). According to Rushton (1997) it may occur at any age but its beginning is most commonly observed in the third decade of life. Arant (1991) diagnosed arterial hypertension in 20% of children with post-inflammatory nephropathy and the majority of them was over 5 years of age. In Polish children aged 7 -10 years with post-inflammatory nephropathy, the prevalence of arterial hypertension was approximately 50% (Wyszynska & Litwin, 2000). In children with obstructive nephropathy, arterial hypertension seems to be sodium-dependent and occurs more commonly when urinary tract obstruction is bilateral.

A late consequence of post-inflammatory nephropathy may be urolithiasis which was observed in 18% patients with renal scarring (Kohler et al., 2003; Vachvanichsanong, 2007).

In pregnants with reflux nephropathy, recurrent urinary tract infections, arterial hypertension, gestosis and/or renal failure may occur (Vachvanichsanong, 2007) therefore they are at risk for spontaneous abortion and premature delivery. Increased mortality of newborns from these mothers was observed.

4. Diagnosis of post-inflammatory nephropathy

Diagnostics of post-inflammatory nephropathy include laboratory and imaging studies. Initially, urinalysis may be normal or may show sparse proteinuria and/or microhematuria. Proteinuria may gradually increase with time. Slightly decreased ability to concentrate and acidify urine may also be observed (Polito et al., 1999; Seidel et al., 1993).

An acetyl-beta-D-glucose aminidase and β2-microglobulin are a widely used markers of tubulointerstitial fibrosis. Recently, early and more specific markers of tubulointerstitial fibrosis have been introduced such as neutrophil gelatinase-associated lipocalin (NGAL) (Ichnio et al., 2010; Wasilewska et al., 2011), kidney injury molecule-1 (KIM-1) (Wasilewska et al., 2011], type IV collagen and gluthatione S-transferases alpha and pi (GST-α and GST-π) (Cawood et al., 2010, Branten et al., 2000). GST-α is a marker of proximal tubular injury

whereas GST-π –distal tubular injury. Chromek et al. (2003, 2004) recommended ratios of MMP-1, MMP-2 and MMP-9 to their tissue inhibitors TIMP-1 and TIMP-2 as markers of tubulointerstitial fibrosis.

Valuable diagnostic clues are provided by radiologic evaluation, including ultrasonography, static renoscintigraphy (99mTc DMSA) and dynamic renoscintigraphy (99mTcDTPA, 99mTcEC, 99mTcMAG-3). Urography and voiding cystourethrography (VCUG) are also helpful.

Kersnik et al. (2002) evaluated ultrasonography efficacy in detection of renal scarring. They demonstrated that sensitivity of ultrasonography in detection of benign, moderate and severe renal scarring was 34.1%, 79.2% and 100%, respectively. The study by Moorthy et al. (2004) revealed that in detection of renal scarring, ultrasonography was characterized by higher specificity (91.8%) and lower sensitivity (47.2%) as compared to static renoscintigraphy. At present, ultrasonography still remains an important tool in evaluation of renal scarring.

The advent of static renoscitigraphy using dimercaptosuccinic acid labeled by 99m technetium (99mTcDMSA) was a turning-point in diagnostic evaluation of post-inflammatory nephropathy. 99mTcDMSA is thought to be the gold standard for detection and monitoring of renal scarring. 99mTcDMSA undoubtedly contributes to expansion of our knowledge concerning pathogenesis of post-inflammatory nephropathy (Gordon, 1987; Orleana et al., 2004; Rushton, 1997; Shapiro et al., 1988; Smellie, 1985; Stokland et al., 1996). On the basis of 99mTcDMSA, the classification of severity of renal scarring was made (Fig. 3.) (Goldraich et al., 1983).

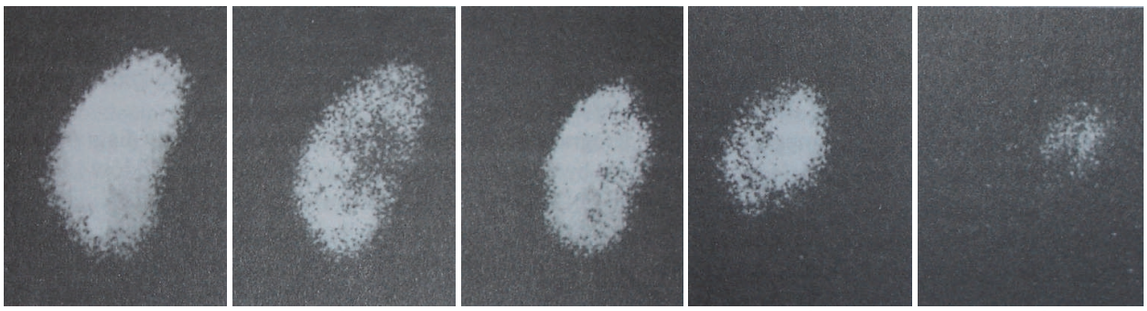

Fig. 3. Classification of renal scarring according to findings at 99mTcDMSA renal scan: 0 – normal, 1° - no more than 2 scarred areas, 2° - more than 2 scars with some areas of normal parenchyma, 3° - generalized damage to the whole kidney, 4° - cirrhotic kidney with little or no uptake of DMSA.

Dynamic renoscintigraphy also has potential to detect renal scarring reliably (Gad et al., 2004; Narayana et al., 2004). In addition, it evaluates renal function as well as status of pelvicalyceal systems and ureters. In dynamic renoscintigraphy, diethylene triaminepentaacetic acid (DTPA), ethylenodicysteine (EC), and mercaptoacetyltriglycerin (MAG-3) labeled by 99m technetium are used.

Nowadays, urography is performed less commonly because there are more effective methods of urinary system visualization. In addition, urography is viewed as more harmful than beneficial for patients. Urography enables to evaluate renal size and margins. It also visualizes pelvicalyceal systems and ureters and thus has potential to detect anatomical obstruction location.

VCUG is performed in order to detect vesicoureteral reflux and anatomical anomalies of the bladder and urethra. In the presence of vesicoureteral reflux, VCUG may demonstrate dilation and deformity of renal calyces and occasionally intrarenal refluxes. VCUG may give only a suspicion of post-inflammatory nephropathy. VCUG visualizes the bladder and urethra and thus has potential to detect anatomical obstruction to urine flow. Instead of VCUG videocystometry is more and more commonly performed because it is able to detect both vesicoureteral reflux and anatomical/functional abnormalities of lower urinary tract.

5. Management of post-inflammatory nephropathy

Management of post-inflammatory nephropathy include therapy and prophylaxis of urinary tract infection, correction of anatomical and functional abnormalities of urinary tract and nephroprotection based primarily on inhibition of production or activity of TGF-β. Nowadays, a proven nephroprotective activity is displayed by angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (Khalil et al., 2000, Wang et al., 2005), aldosterone antagonists (eplerenone), renin inhibitors (aliskiren) and anti-oxidants (α-tocopherol) (Chan et al., 2001; Cojocel et al., 2005; Saborio et al., 2000).

Novel drugs which inhibit tubulointerstitial fibrosis include low-molecular leucine-rich proteoglycans, decorin, and biglycan. They have potential to permanent bond with TGF-β and thus they inhibit its activity (Solari et al., 2005). Inhibition of tubulointerstitial fibrosis was also observed after blockade of type II TGF-β receptor (Jernigan et al., 1996; Kasuga et al., 2001; Kushibiki et al., 2005) and as a result of therapy with antibodies against TGF-β (Gagliardini & Benigni, 2006). Inhibition of activity of tissue transglutaminases which participate in activation of TGF-β may be a therapeutic option in patients with post-inflammatory nephropathy in future (Shweke et al., 2008). Other factors which are likely to inhibit tubulointerstitial fibrosis are hepatocyte growth factor (HGF) (Mizuno et al., 2001) and bone morphogenic protein 7 (BMP-7) (Kopp, 2002). The latest studies demonstrated nephroprotective activity of Lefty-A which inhibits and even reverses transformation of tubular cells into myofibroblasts (Li et al., 2010, Yao et al., 2011).

6. Serum concentrations of selected cytokines in children with reflux and obstructive nephropathy – original studies

The purposes of the study were - to assess serum TGF-β_1, TNF-α, IL-1 β, IL-6 and IL-8 levels in children with post-inflammatory nephropathy (reflux and obstructive nephropathy), - to compare serum TGF-β_1, TNF-α, IL-1 β, IL-6 and IL-8 levels between children with unilateral and bilateral vesicoureteral reflux, and between those with vesicoureteral reflux of high and low grade, - to compare serum TGF-β_1, TNF-α, IL-1 β, IL-6 and IL-8 levels between children with and without hypertension, and between those with and without proteinuria.

Patients and methods: The study comprised 70 children (24 boys and 46 girls) aged 1-17 years with renal scarring diagnosed scintigraphically. All children had a history of recurrent urinary tract infections including at least one episode of acute pyelonephritis. Vesicoureteral reflux and unilateral ureteropelvic/vesicoureteric junction obstruction were detected in 85.7% (60/70) and 14.3% (10/70) of children, respectively. Arterial hypertension was diagnosed in 17.2% (12/70) of patients. Proteinuria was observed in 25.7% (18/70) of children. Renal insufficiency developed in 5,7% (4/70) of patients. Serum TGF-β_1, TNF-α, IL-1 β, IL-6 and IL-8 concentrations were measured by ELISA.

Results: In children with reflux/obstructive nephropathy, the mean serum TGF-β_1 and IL-1β concentrations were significantly lower than in controls. Similarly, serum IL-8 concentrations were lower in both studied groups than in controls but the differences were not statistically significant. There were no statistically significant differences in the mean serum TNF-α and IL-6 concentrations between children with reflux/obstructive nephropathy and controls.

There were no statistically significant differences in the mean serum TGF-β_1, TNF-α, IL-1 β, IL-6 and IL-8 levels between children with unilateral vesicoureteral reflux and those with bilateral vesicoureteral reflux. There were also no statistically significant differences in the mean serum TGF-β_1, TNF-α, IL-1 β, IL-6 and IL-8 levels between children with vesicoureteral reflux of high grade and those with vesicoureteral reflux of low grade.

Statistically significant differences in the mean serum TGF-β_1, TNF-α, IL-1 β, IL-6 and IL-8 levels between children with arterial hypertension and the remaining patients were not observed.

In children with proteinuria, the mean serum TGF-β_1 level was significantly lower than in the remaining patients. There were no statistically significant differences in the mean serum TNF-α, IL-1 β, IL-6 and IL-8 levels between children with proteinuria and the remaining patients.

7. Conclusions

1. The low serum TGF-β_1 and IL-1β concentrations in patients with reflux and obstructive nephropathy seems to be a result of increased influx of this cytokines into renal parenchyma and/or increased urinary TGF-β_1 and IL-1β excretion due to tubular damage associated with nephropathy.
2. The lower serum concentration of TGF-β_1 in patients with proteinuria secondary to post-inflammatory nephropathy may confirm participation of this factor in progression of nephropathy

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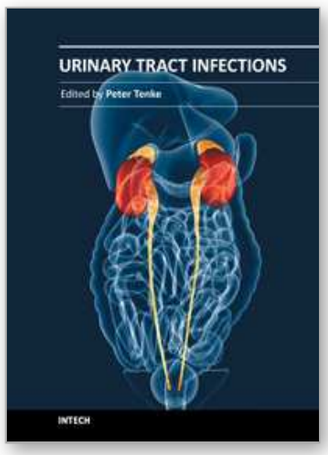

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Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, and they are also the leading cause of hospital-acquired infections. Therefore, the appropriate management of UTIs is a major medical and financial issue. This book covers different clinical manifestations of UTI, with special emphasis on some hard-to-treat diseases, and special conditions in respect of treatment; antibiotic resistance and the available alternative strategies for the prevention and treatment of UTIs and it deals with urinary tract infections in children. The aim of this book is to give a summary about the different aspects of the diagnosis, management and prevention of urinary tract infections for all medical disciplines.

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